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Tissue ACE inhibition and sodium status in left ventricular dysfunction

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Summary

Left ventricular (LV) dysfunction is characterized by a progressive loss of cardiac pump function, which eventually leads to the clinical syndrome of chronic heart failure (CHF). Heart failure is associated with high morbidity and mortality. The incidence of heart failure has increased during the last decades, mainly because improved survival after acute myocardial infarction.

Renin angiotensin aldosterone system (RAAS) activation plays a major role in the progression of left ventricular dysfunction towards chronic heart failure. Angiotensin-converting enzyme (ACE) inhibition therapy improves cardiac function and reduces morbidity and mortality.

Although ACE-inhibition slows the gradual progression of myocardial dysfunction towards overt CHF, it does not prevent it. In order to reach maximal therapy response to ACE inhibition a low sodium intake may be required. The expected underlying mechanism was that an activated RAAS – i.e. elevated renin production – induced by sodium restriction is required for an optimal therapeutic response to ACE inhibition. Hence, the first main subject of this thesis was to study intervention with the sodium balance in order to optimize ACE-I therapy. In **chapter 2** we describe the effects of dietary salt restriction on ACE inhibitor treatment in rats with myocardial infarction, after 10 weeks of follow-up. Whereas dietary salt restriction alone did not worsen or improve any of the studied parameters, it augmented left ventricular –but not renal or plasma- ACE inhibition with zofenopril. This further reduction of ACE activity was associated with a more potent anti-hypertrophic effect of the drug. Although LV hypertrophy reduction with zofenopril was improved by dietary salt restriction, we did not find a further improvement of *in vitro* cardiac function.

We subsequently studied whether on the long term dietary salt restriction may improve the outcome of long term ACE inhibition therapy. Therefore, we studied mortality during a period of 14 months, and *in vivo* cardiac function. The results are described in **chapter 3**, and show that during 14 months of treatment with the ACE inhibitor quinapril dietary sodium restriction did not improve survival or cardiac function in rats with myocardial infarction. Based on these results, we question the benefit of dietary sodium restriction during long-term ACE inhibition for post-infarct left ventricular dysfunction. More encouraging results were obtained with addition of a diuretic (hydrochlorothiazide) to quinapril treatment. This pharmacological strategy to induce a negative sodium balance was also studied, as it is easier to maintain for the patient, and already commonly used in the cardiologic practice to reduce symptoms of fluid retention. We showed an improvement in survival and cardiac function during the first 8 months of follow-up. However, towards the end of follow-up period (14 months), the beneficial effects of hydrochlorothiazide waned off. This discrepancy between early beneficial effects and loss of benefit towards the end of long-term treatment is further discussed below, but first we focused on short-term effects of hydrochlorothiazide on ACE-I therapy.

In **chapter 4** we investigated whether the (early) benefits of adding hydrochlorothiazide to ACE inhibition could be explained by a pharmacokinetic interaction. We observed

that indeed the diuretic caused accumulation of two different ACE inhibitors. The hydrophilic ACE inhibitor lisinopril accumulated in plasma, whereas the lipophilic ACE inhibitor zofenopril accumulated mainly in heart and kidney tissue. We showed that the most likely mechanism is a hydrochlorothiazide-induced volume depletion, either directly or via a GFR decrease leading to reduction in renal clearance of the ACE inhibitors. The potential risk of this loss of kidney function is the main issue in **chapter 5**. Here we show that combining hydrochlorothiazide with quinapril caused an increase in plasma creatinine, which indicates decreased renal function. Furthermore we showed that increased plasma creatinine concentrations measured after 4 months of treatment were significantly associated with increased mortality in rats with myocardial infarction towards 14 months of follow-up. Furthermore, histopathology showed that addition of hydrochlorothiazide to quinapril in rats with myocardial infarction caused tubular degeneration as well as inflammation and fibrotic lesions in renal proximal tubular interstitium. From this study we conclude that during long-term treatment post-MI combining ACE inhibition with a diuretic can cause renal abnormalities, which could cancel out the early beneficial effects of addition of a diuretic to ACE inhibitor therapy.

Second main topic of this thesis was to study the consequences of ACE inhibitor withdrawal on cardiac function and neurohormones, and endothelial function. In contrast to the well-studied beneficial effects of ACE inhibition therapy itself, remarkably little has been published about the consequences of its withdrawal. In **chapter 6** we report progressive left ventricular hypertrophy and activation of the renin-angiotensin-aldosterone system after 4 and 6 weeks of ACE inhibitor withdrawal. Secondly, we found that substantial endothelial dysfunction, which plays a central role in the pathophysiology of heart failure, developed within 4 weeks after cessation of therapy.

In **chapter 7**, we studied the involvement of nitric oxide (NO) and endothelium-derived hyperpolarizing factor (EDHF) in the vascular effects of the ACE-I quinapril and its withdrawal. We showed that long-term ACE inhibition in rats with myocardial infarction markedly improved non-NO/prostanoid-mediated (i.e. EDHF-mediated) endothelium-dependent vasorelaxation. Within four weeks after treatment withdrawal this beneficial effect completely disappeared. These findings highlight the potential importance of EDHF impairment in development of endothelial dysfunction after myocardial infarction, and the possibility to improve EDHF-mediated vasodilation with chronic ACE inhibitor therapy.

The observed alterations after withdrawing long-term post-MI quinapril treatment in the present study may account for an increased risk for ischemic events. By that our findings highlight the potentially harmful effects associated with abrupt discontinuation of long-term post-MI ACE inhibition, and imply careful clinical consideration in this matter.

Chapter 8 provides a final overview on the issue of sodium depletion to augment tissue ACE inhibition. Sodium restriction or diuretic therapy per se does not influence the progression of LV dysfunction into chronic heart failure, with the exception of aldosterone receptor antagonists. Furthermore, it seems improbable that on the long-

term sodium depletion will substantially improve prognosis of patients with myocardial infarction treated with ACE inhibition in an optimal dose. Although addition of sodium restriction improved intermediate parameters in rats with myocardial infarction, treatment outcome was not altered. Diuretic treatment improved early chronic survival and cardiac function. Thus long-term treatment with this diuretic in combination with ACE inhibition after myocardial infarction may be safe, as far as animal experiments can be extrapolated to humans. As long-term survival was similar in rats treated with ACE-I alone and combined with hydrochlorothiazide, the balance between beneficial and adverse effects of adding diuretics to ACE inhibition therapy thus far ends up undecided.
